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EXPOSURE-BASED COGNITIVE BEHAVIOR THERAPY FOR ATRIAL FIBRILLATION: A NOVEL TREATMENT PARADIGM

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Exposure-based cognitive behavior therapy for atrial fibrillation: A novel treatment paradigm

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To those whose hearts beat to a different rhythm.

ABSTRACT

Background: Atrial fibrillation (AF) is a prevalent arrhythmia associated with symptoms such as irregular heartbeat, palpitations, dyspnea, chest pain and fatigue. In many patients, AF symptoms are not alleviated by current treatment strategies and there is a clinical need for better symptom management. AF is associated with low quality of life (QoL) and psychological distress, and patients often present with symptom preoccupation; i.e., fear of AF symptoms and avoidance behavior. Symptom preoccupation may play an important role in AF disability and is associated with higher self-reported symptom severity and low QoL.

Aims: The overall objective of this doctoral project is to develop and evaluate a novel, AF-specific, exposure-based internet-delivered cognitive behavior therapy (AF-CBT) protocol to increase QoL and potentially reduce symptom burden in patients with symptomatic paroxysmal AF. The specific aims consist of the following:

- investigate the feasibility, acceptability and potential efficacy of a novel treatment protocol of exposure-based AF-CBT delivered face-to-face (Study I) or via the Internet (Study II);
- investigate the efficacy of internet-delivered exposure-based AF-CBT compared to a waitlist receiving standardized AF education (Study III);
- investigate if reduction in symptom preoccupation, i.e., cardiac-related fear, hypervigilance and avoidance behavior, mediates the therapeutic effect of AF-CBT (Study IV).

Methods: The feasibility, acceptability and potential efficacy of the AF-CBT protocol were evaluated in two uncontrolled pilot studies (Study I and II). The treatment's efficacy was further investigated in a randomized controlled trial (RCT), where a total of 127 participants were randomized to 10 weeks of AF-CBT (n=65) or to a waitlist offered standardized AF education (AF-EDU; n=62 (Study III)). All participants were diagnosed with paroxysmal symptomatic AF and were referred by a cardiologist (Study I and II) or self-referred (Study III). The participants underwent thorough cardiac evaluations and psychological assessments to ensure that they received medical treatment according to current guidelines. The treatment was therapist-guided exposure-based AF-CBT delivered face-to-face (Study I) or over the Internet (Study II and III) for 10 weeks. The treatment targeted two proposed maintaining factors of AF disability: fear of AF symptoms and AF-related avoidance behavior. The primary outcome was AF-specific QoL and secondary outcomes included, among others, self-reported AF symptoms, symptom preoccupation, general QoL, depression, stress, healthcare utilization and objective AF burden measured by electrocardiogram (ECG). In order to explore potential mediators of the treatment effect, data from the RCT was used to conduct a mediation analysis, with weekly assessments of three putative mediators (cardiac-related fear, hypervigilance and avoidance behavior) and treatment outcome (AF symptoms and disability (Study IV)).

Results: AF-CBT rendered high adherence, satisfaction and treatment completion (Study I-III). We observed large to medium effect sizes, with stable effects six-months after the treatment (Study I and II). In Study III, AF-CBT led to large and superior between-group improvement in AF-specific QoL (primary outcome) three months after the treatment. Significant improvements were also observed on all relevant outcomes in favor of AF-CBT. The results were sustained 12 months after the treatment. No significant difference in objective AF burden between the groups at three-month follow-up was detected. The analysis of mediators showed that a reduction in symptom preoccupation, i.e., cardiac-related fear, hypervigilance and avoidance behavior mediated the treatment effect of self-reported AF symptoms and disability.

Conclusion: Internet-delivered exposure-based AF-CBT is feasible, acceptable and clinically effective for patients with AF. The results support a treatment strategy targeting symptom preoccupation via exposure-based CBT to reduce AF symptoms and disability. AF-CBT administered via the Internet has the capacity to ameliorate the well-being of a large group of patients that do not achieve satisfactory improvement from current treatment methods.

LIST OF SCIENTIFIC PAPERS

I. Särnholm[*] J, Skúladóttir[*] H, Rück C, Pedersen SS, Braunschweig F, Ljótsson B. Exposure-Based Therapy for Symptom Preoccupation in Atrial Fibrillation: An Uncontrolled Pilot Study. *Behavior Therapy*. 2017 Jun;:1–14.
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II. Särnholm J, Skúladóttir H, Rück C, Klavebäck S, Ólafsdóttir E, Pedersen SS, Braunschweig F, Ljótsson B. Internet-Delivered Exposure-Based Therapy for Symptom Preoccupation in Atrial Fibrillation: Uncontrolled Pilot Trial. *JMIR Cardio.* 2021 Mar 2;5(1):e24524.

III. Särnholm J, Skúladóttir H, Rück C, Axelsson E, Bonnert M, Bragesjö M, Venkateshvaran A, Ólafsdóttir E, Pedersen SS, Ljótsson[*] B, Braunschweig[*] F. Internet-delivered Cognitive Behavioral Therapy for Symptom Preoccupation in Atrial Fibrillation: A Randomized Controlled Trial. (Manuscript).
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IV. Särnholm J, Axelsson E, Skúladóttir H, Bonnert M, Bragesjö M, Rück C, Pedersen SS, Braunschweig F, Ljótsson B. The role of Cardiac-related Fear, Hypervigilance and Avoidance Behavior in Exposure Therapy for Atrial Fibrillation: A Mediation Analysis. (Manuscript).

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
AF-CBT	Cognitive behavior therapy for atrial fibrillation
AF-EDU	Atrial fibrillation education waitlist
AFEQT	Atrial Fibrillation Effect on Quality of Life
CBT	Cognitive behavior therapy for atrial fibrillation
CSQ-8	Client Satisfaction Questionnaire
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
IBS	Irritable bowel syndrome
RCT	Randomized controlled trial
QoL	Quality of Life

1 INTRODUCTION

The rhythm of our hearts affects our mental and emotional experiences, and the communication between the heart and brain is an ongoing, dynamic dance, with each organ continuously influencing the other's function (1). With atrial fibrillation (AF), the heartbeat is often chaotic and it is understandable that AF patients respond with negative emotions and behavioral adjustments to that chaos. This quite often leads to a vicious cycle of fear and avoidance, where AF dictates the rhythm of the patient's life.

AF is a prevalent arrhythmia and many patients experience disabling symptoms and impaired quality of life. There are few easily accessible and effective treatment options available to alleviate AF. There is a bidirectional relationship between mental health and cardiovascular diseases (2), and psychological factors are known to play a role in the clinical course in AF, although patients with AF are rarely assessed or considered for psychological treatment.

My interest in exploring the interplay of psychological factors in somatic diseases emerged during my practice as a clinical psychologist, where I often treated psychological conditions comorbid with somatic disorders. Most commonly, the physical and mental aspects of patients' health were treated as two separate units within the healthcare system. During the course of my doctoral education I have found it instructive and rewarding to work towards bridging this gap and expanding cognitive behavior therapy (CBT) for a new patient group.

This thesis describes how I, together with my supervisors and colleagues, developed and evaluated a novel CBT treatment for AF and how we explored psychological factors in AF. The results are limited by design and methods, but hopefully this thesis will mark the start of a journey continuing to bring the heart and mind closer in clinical practice for the benefit of a large patient group.

Stockholm, May 2021

2 BACKGROUND

2.1 ATRIAL FIBRILLATION

2.1.1 What is atrial fibrillation?

Atrial fibrillation (AF) is caused by disturbances of electrical signaling in the two upper heart chambers (atria). During AF, electrical activity in the atria is chaotic, resulting in an irregular and often fast activation of the main chambers (ventricles) and dyssynchrony between atrial and ventricular mechanical function (3). Commonly, AF episodes are triggered by rapid electrical activity arising from the pulmonary veins inserting into the posterior wall of the left atrium. When patients have AF, not only do they experience a rapid and irregular heartbeat but also symptoms such as chest pain, dizziness, weakness and shortness of breath that may range from mild to disabling (4). Sometimes, however, AF may be asymptomatic. The following illustration shows the electrical signaling during AF.

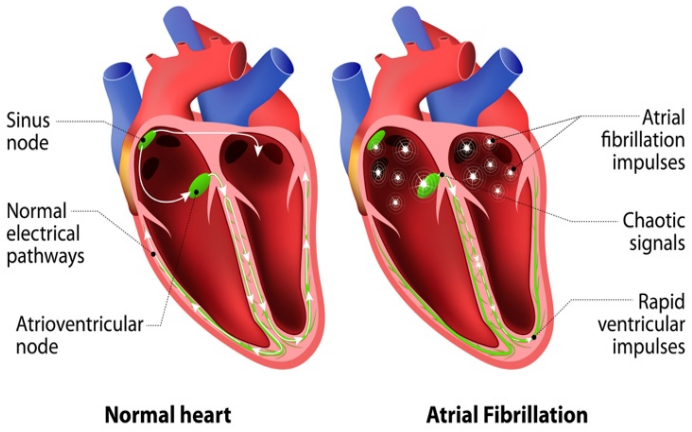

Figure 1. Illustration of the electrical signaling in AF.

2.1.2 Prevalence

AF is the most common arrhythmia with an estimated prevalence of 2-4 % in the general adult population, and the prevalence shows an upward trajectory in the population worldwide (5). Factors contributing to its increase include extended longevity, better detection of AF as well as increased incidence of other cardiovascular risk factors predisposing to AF (6). Advanced age is a major risk factor for AF, and the corresponding prevalence for patients older than 80 years is approximately 10% (7). The prevalence of AF is lower in women, but the risk for complications, such as stroke, is similar or even higher compared with men with AF (6,8).

2.1.3 Diagnosis and classification of AF

A rhythm documentation using an 12-lead electrocardiogram (ECG) or recording of a rhythm strip lasting for at least 30 seconds is required to diagnose AF (9). AF is classified based on its pattern, duration and how or when it may or may not convert back to normal cardiac rhythm. The classification of paroxysmal AF implies that the AF episodes are intermittent, commonly start suddenly and last briefly or for days and then convert back to normal cardiac rhythm within seven days. The classification of persistent AF suggests that the arrhythmia does not self-terminate and requires medical procedures, such as cardioversion, to restore normal cardiac rhythm (10). Patients who have had continuous AF for more than one year receive a diagnosis of permanent AF (10). The natural course of AF is that it often progresses from paroxysmal to permanent, which means that the AF burden increases over time, with AF episodes becoming more frequent or of longer duration (11).

AF episodes may be both symptomatic, where the patient can feel symptoms of AF, and asymptomatic, also referred to as "silent AF". It is also common for patients to experience both symptomatic and asymptomatic AF episodes (12). Since AF can lead to stroke and other severe health consequences, an early diagnosis and screening of risk groups is important to identifying asymptomatic AF (13).

2.1.4 Etiology

Current evidence suggests that the etiology of AF is caused by multiple interacting factors, such as hereditary components, and clinical risk factors predisposing for AF, such as advanced age, diabetes mellitus, hypertension, valve disease, congestive heart failure, obesity and obstructive sleep apnea (14). A sedentary lifestyle has been associated with an increased risk for AF; interestingly, extreme levels of physical activity, for example endurance sports, confers an elevated AF risk as well (15). A common pathophysiological pathway of these conditions is that they are associated with enlargement or fibrotic remodeling of the atria, thus providing a biological and structural substrate facilitating the initiation and perpetuation of AF (3). Furthermore, there is also emerging evidence suggesting that psychological conditions, such as post-traumatic stress disorder, are associated with an elevated risk of developing AF (16).

2.1.5 Mortality and morbidity

Although the arrhythmia itself is not lethal, it is associated with a substantially increased risk for all-cause mortality (due to associated comorbidity, such as heart failure) (17) and morbidity such as acute coronary syndrome and stroke (18). AF is also associated with anxiety disorders and depression (19) as well as with high rates of healthcare utilization and hospitalization, leading to an increased economic burden on society (20). Healthcare utilization and cost has also been shown to vary according to the clinical course of AF, and has been shown to be markedly higher in paroxysmal AF patients compared with those with permanent AF (21).

2.1.6 Quality of Life

AF significantly impairs quality of life (QoL) in a large proportion of patients. AF patients have both lower QoL compared with healthy controls (22) and are also comparably disabled or more disabled than patients with structural heart disorders, such as heart failure (23). Low QoL in AF is also associated with a higher risk for hospitalization (23). In a study using data from a large community-based AF registry, several patient factors were shown to be associated with low QoL including younger patients, women and patients with comorbid diseases, such as obstructive sleep apnea and hypertension. Patients with new onset of AF were shown to have lower QoL than those with permanent AF, whereas paroxysmal and persistent AF did not show to differ in QoL (24).

2.2 PSYCHOLOGICAL FACTORS IN AF

A factor that has been shown to impact QoL and AF disability is how patients interpret and perceive their AF symptoms (25). QoL in AF has also been shown to be impaired irrespective of arrhythmia burden (duration and frequency of symptoms) when measured objectively (26, 27), suggesting that symptoms and their impact extend beyond the objective arrhythmia burden and anticipation of disruptive symptoms may have a depressant effect on QoL. AF can be divided in to either *objective AF burden*, measured by ECG monitoring, or *subjective AF symptoms*, measured by self-report. When investigating the relationship between objective AF episodes, recorded by ECG and patients' subjective perceptions of AF symptoms, it has been shown that it is difficult for patients to correctly estimate their AF burden. Concurrent mood disorder and psychological distress have been linked to patients overestimating their actual AF burden (28). Furthermore, a study by McCabe et al. (29) showed that patients with recurrent AF, who perceived their symptoms as unpredictable and potentially leading to serious health consequences, reported increased psychological distress compared with patients with more understanding of the diagnosis and less perceived negative consequences.

2.2.1 Anxiety, depression and perceived stress

Psychological factors have a bidirectional relationship with AF, where symptoms may lead to a deterioration in mental health that, in turn, may have a negative effect on the short- and long-term clinical course. Many studies have concluded that depression and anxiety are elevated in AF patients, with estimates ranging from 25 to 50% (30). In a study by Thrall et al. it was found that 38% of patients with AF had elevated levels of depression, measured by the Beck Depression Inventory, and the same number corresponded to elevated anxiety according to the State-Trait Anxiety Inventory (31). The levels of depression in AF were comparable to patients with other chronic diseases, while the levels of anxiety were found to be significantly higher in AF than in other patient groups living with chronic diseases.

Anxiety and depression also lead to an increase in perceived intensity of AF symptoms and more healthcare seeking irrespective of objectively measured AF burden (28). Depression has been shown to be a significant predictor of AF recurrence following cardioversion (32) and has been associated with increased cardiovascular mortality in patients with AF (33). Furthermore,

enhanced stress has been found to trigger and increase the risk for recurrent symptomatic AF episodes (34). Stress is frequently reported as a trigger for AF by patients in clinical settings and research (35) and has also been associated with elevated levels of anxiety and depression (29).

2.2.2 Symptom preoccupation: an AF-specific psychological approach

In summary, anxiety and depression are common comorbid conditions in AF affecting QoL and potentially the clinical course of AF. However, previous research does not explain how AF-specific psychological factors may lead to development of AF-related disability. This doctoral project aims to explore a more disease-specific approach by defining AF-related psychological factors in terms of cardiac-related fear and avoidance behaviors. The discordance between objective AF episodes and perceived AF symptoms and the relationship between psychological factors and perceived symptom burden suggest that *symptom preoccupation* may play a role in the development of AF disability. Symptom preoccupation in AF has been shown to be associated with increased symptom burden, depression and anxiety, and poor QoL (36). Interestingly, these findings are similar to those described in other somatic and functional disorders, such as chronic pain and irritable bowel syndrome (IBS), where symptom preoccupation has been shown to be associated with symptom severity, functional disability, healthcare seeking, depression and anxiety (37). We have further conceptualized symptom preoccupation in AF as A) fear of starting and experiencing AF episodes; B) hypervigilance to cardiac and AF-related symptoms; C) worry about cardiac health and potential complications (e.g., stroke); and D) AF-related avoidance behavior; e.g., avoidance of social or physical activities (38,39). Symptom preoccupation in AF, with the assumption that cardiac-related fear and avoidance behavior leads to a disproportionate AF disability, can be described as an analogue to the fear/avoidance model of chronic pain (40), where the individual's interpretation of bodily pain leads to long-term maladaptive avoidance responses and impairments (41). Two of the main psychological components in symptom preoccupation are described below.

2.2.2.1 Cardiac-related fear and hypervigilance

As mentioned earlier, AF patients show a poor correlation between subjectively perceived AF symptoms and objectively measured AF episodes (26,27). Thus, AF patients frequently misinterpret cardiac activity related to stress or physical exertion as arrhythmia (i.e., hypervigilance). For patients with AF, both AF symptoms and normal cardiac activation may be conditioned with fear or negative emotional responses through respondent conditioning (42). This kind of interoceptive conditioning has been found to play a key role within panic disorders, but also in patients with, for example, non-cardiac chest pain (42) where bodily sensations, such as a slight change in heart rate or breathlessness, may trigger a fear response. In experimental research, interoceptive conditioning has been found to enhance the perception and reaction to bodily symptoms (43), meaning that the fear and hypervigilance towards cardiac-related symptoms may also make the patient more prone to react with anxiety. The anxiety leads to an increase in arousal in the autonomic nervous system and heart rate which,

in turn, can start extra beats and potentially AF episodes (44). Anxiety has been shown to be a predictor of AF, where multiple studies have indicated an association between elevated levels of anxiety and the recurrence of AF symptoms (45). Thus, the enhanced fear and hypervigilance of cardiac symptoms lead to increased subjective symptom burden and when patients react with fear they may even trigger AF symptoms.

2.2.2.2 AF-related avoidance behavior

In a qualitative study by McCabe et. al (46), symptom preoccupation in patients living with AF was highlighted. One prominent theme was their fruitless attempts to control the onset of AF by avoiding certain situations or activities. Patients described the inability to control symptom onset as distressing, leading to increased control behaviors by, for example, seeking the cause of recurrent AF episodes. Despite making adjustments in everyday life, the patients were often still not able to avoid recurrent episodes of AF, which caused distress and the perception of a personal failure (46). AF-related avoidance behavior serves to decrease anxiety and cardiac-related symptoms and is developed and maintained through operant conditioning (42). Avoidance behavior in AF can include overtly avoiding physical activities or social situations where symptoms are unwanted or by monitoring one's heartbeat or trying to distract oneself from the heart (47). When AF patients avoid social and physical activities while experiencing symptoms or in anticipation of symptoms, they also maintain their fearful responses to AF symptoms, as commonly seen in anxiety disorders (48). AF patients also become more impaired in the long run as well as more preoccupied with their symptoms and prone to developing depression (49). In summary, avoidance behavior contributes to a sustained fear of AF-related symptoms as well as disability, impairment and decreased QoL.

A clinical model of the proposed role of symptom preoccupation in AF is illustrated in Figure 2. Notably, the empirical data that underlie Figure 2 have only been collected in cross-sectional studies. Therefore, no firm causal conclusions about the directionality of the associations between symptom preoccupation and AF burden can be made.

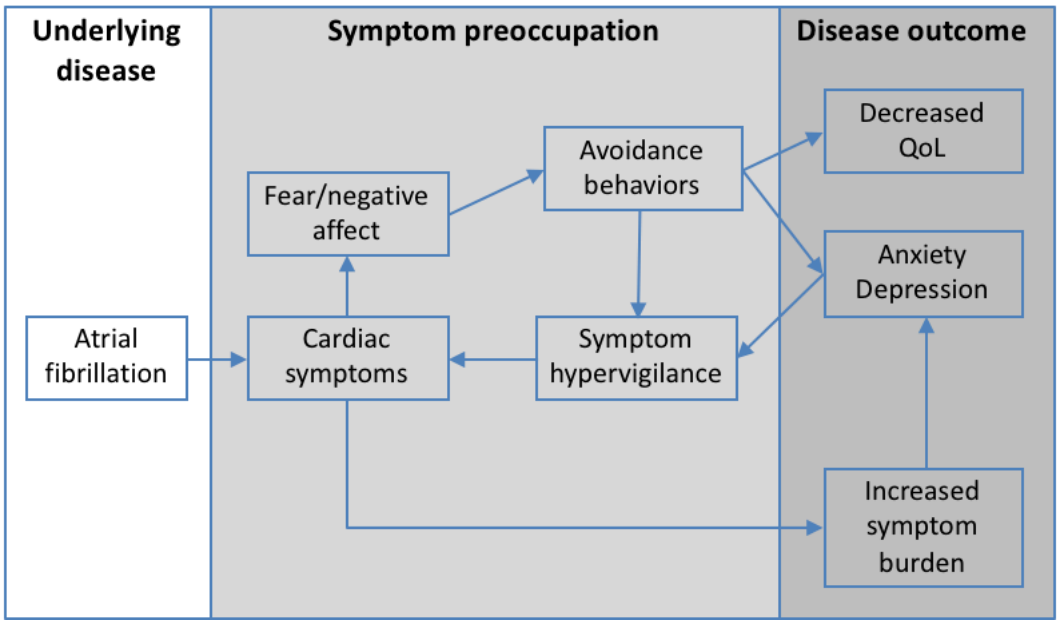

Figure 2. The role of symptom preoccupation in AF.

2.3 CLINICAL STRATEGIES IN ATRIAL FIBRILLATION

2.3.1 Pharmacological and invasive therapy

As AF is a chronic disease and few interventions have been shown to sufficiently eliminate AF, the treatment of AF focuses on preventing thromboembolic complications, controlling symptoms and improving or preserving patients' QoL.

Most importantly, patients with AF have an increased risk of stroke or other thromboembolic events. Therefore, treatment guidelines for AF (50) recommend prophylactic oral anticoagulation to reduce the risk for stroke in those with additional risk factors (51). Furthermore, heart rate-controlling medications, such as betablockers, and rhythm-control strategies, such as cardioversion, antiarrhythmic drugs and catheter ablation to maintain and restore normal cardiac rhythm, are used to improve symptoms (50).

Catheter ablation of AF is a well-established invasive treatment to prevent recurrent AF and reduce AF-related symptoms. In general, it is used as second-line treatment after antiarrhythmic medication intolerance, for example. The outcome of the procedure has been difficult to predict in individual patients, and it is also common that patients need more than one procedure to alleviate symptoms (52). Catheter ablation has been shown to be more effective than medical therapy in re-establishing sinus rhythm, but its long-term effect on QoL has been more uncertain (52). Recent studies show promising effects of catheter ablation on QoL, where the procedure on patients with AF compared to antiarrhythmic medication led to greater and sustained improvements in QoL 12 months after treatment (53,54). Prophylactic anticoagulation has shown to reduce mortality in AF patients by reducing risk for stroke, but interventions for rhythm control have less clear long-term mortality benefits

(55). Emerging evidence indicates that in newly diagnosed symptomatic AF patients, early rhythm control interventions, such antiarrhythmic drugs and catheter ablation, are associated with lower risk for cardiovascular complication (56). Based on these findings, catheter ablation is the treatment of choice in patients with drug refractory symptomatic paroxysmal or persistent AF or based on patient preference.

Despite improvements in the management of AF, current treatment strategies (pharmacological and invasive therapies) do not adequately alleviate symptoms in many patients with AF, and may also be associated with potentially serious side effects (57,58). With few easily accessible and effective treatment options available, AF places substantial demands on the healthcare system and there is a clear need for additional strategies to manage AF symptoms.

2.3.2 Non-medical strategies to promote well-being

Health care providers are recommended to educate their patients on the nature of AF, available treatment options and self-care activities, such as being physically active to prevent the progress of cardiovascular disease and to enhance well-being (59). Patient education that is commonly offered in routine care for AF has been associated with improved outcomes (60), and patients that are well-informed of their AF report more acceptance of their diagnosis, fewer symptoms and negative emotions related to their condition (61). This suggests that promoting patient education, understanding of AF and strategies to handle the symptoms could have a positive impact on both QoL and perceived symptom burden. Another factor that has been linked to increased well-being for AF patients is moderate physical activity, which is associated with reduced AF symptoms and increased QoL (62). Medical yoga has also been shown to improve QoL and decrease blood pressure in patients with paroxysmal AF and has been suggested to be used as a self-management strategy (63).

2.4 PSYCHOLOGICAL TREATMENT

2.4.1 Cognitive behavior therapy

Cognitive behavior therapy (CBT) is an established psychological treatment for both psychiatric and somatic conditions (64). Despite recognizing AF as a life-complicating disease associated with both anxiety and depression (35), CBT interventions are understudied in AF. Only two studies have evaluated psychological interventions specifically for AF: one pilot study using a brief intervention of mindfulness interoceptive exposure for AF patients (n=8) showed promising results in decreasing anxiety sensitivity (65); and a couples mindfulness-based CBT-program for AF patients and their spouses showing effects on QoL (66).

The effectiveness of CBT has been investigated in other cardiac conditions. According to a meta-analytical report on face-to-face CBT, cardiac disease treatments commonly consist of a variety of interventions targeting comorbid psychological conditions, such as anxiety and depression, with promising results (67). Stress management interventions, such as relaxation training, have been commonly used for cardiac conditions and have shown beneficial effects on mental and cardiac-related health, although with inconsistent effects across trials (68).

2.4.2 Exposure-based CBT

Exposure-based CBT aims to reduce avoidance behavior, fear of symptoms and associated disability by applying systematic exposure to the stimulus and situations that evoke a fear response (69). Exposure-based CBT is the most empirically supported treatment in treating anxiety disorders, and exposure as a key component in CBT takes interoceptive (internal cues), imaginal or in vivo (external situations) forms (70). Exposure-based CBT, targeting disease-specific anxiety and avoidance behavior using both interoceptive and exposure in vivo techniques accompanied with self-observation exercises, has shown to be effective in somatic functional disorders with regards to physical symptoms and QoL (71,72,73). In exposure therapy, patients are encouraged to broaden their behavioral repertoire in the presence of the feared symptoms or situation (74); e.g., participating in a work event while experiencing cardiac-related symptoms. Furthermore, a strategy to enhance exposure therapy is to use self-observation during exposure (e.g., affect labeling), which has been shown to improve physiological reduction of fear (75). Despite the effectiveness of exposure-based CBT, several barriers for clinicians to deliver exposure based therapy have been identified, such as not wanting to cause distress in patients and applying it to patients with physical comorbidities (76). This suggests that exposure as a clinical treatment strategy might be underused in cardiac patients. Exposure-based CBT has been proven to be a safe option for patients with cardiovascular disease (77), but more clinical trials and interdisciplinary efforts are needed to evaluate the effectiveness of exposure-based therapy applied to cardiac patients. This thesis may contribute to bridging that gap of knowledge by studying exposure-based treatment in a scalable mode of delivery for AF patients.

2.4.3 Internet-delivered CBT

There is a substantial gap between the need for and availability of CBT (78), and by delivering the treatment via the Internet this gap can be somewhat bridged. There are several advantages to internet-delivered CBT, one of them being increased accessibility. The treatment can be made available to patients in rural areas, and patients can access the treatment at flexible hours. Internet-delivered CBT also allows for centralizing the expertise necessary for delivering safe treatments. The mode of delivery enables treatment of a larger number of patients because less therapist time is required per patient (79). Furthermore, since the treatment content is structured it also reduces the effects of therapist drift and non-specific treatment factors (80) and, in general, treatment effects of internet-delivered CBT are similar to those of face-to-face CBT (81).

Internet-delivered CBT has shown effective for a range of somatic and psychiatric disorders (79), but few studies have investigated internet-delivered CBT for cardiac diseases (67) and there has been a demand for increased access to digital interventions within cardiac healthcare (82). Although evidence that internet-delivered CBT for anxiety and depression in cardiac diseases is scarce, two recent randomized controlled trials showed promising results in several outcomes indicating that internet-delivered CBT is both effective and acceptable to cardiac patients (83,84). Internet-delivered CBT has also been evaluated for non-cardiac chest pain,

where patients show fear of bodily symptoms and cardiac disease leading to avoidance behavior, demonstrating comparable results in the reduction in cardiac anxiety and perceived chest pain as in traditional face-to face CBT (85,86).

2.5 SUMMARY OF THE BACKGROUND

AF is a prevalent arrhythmia associated with both somatic and psychological impairments. Symptom preoccupation – i.e., cardiac-related fear and avoidance behavior – may play a role in AF disability. Current treatment strategies do not sufficiently alleviate symptoms in many AF patients, thus developing a multidisciplinary approach to managing AF is warranted. CBT has shown promising effects in other somatic and cardiac disorders but is understudied in AF. In order to improve QoL and psychological and physical functioning in AF patients, we need to further understand mechanisms that drive AF disability and develop effective and scalable treatment options.

3 RESEARCH AIMS

The overall objective of my doctoral project was to develop and evaluate a novel, AF-specific exposure-based, internet-delivered CBT protocol to potentially reduce symptom burden and increase QoL in patients with paroxysmal AF. The studies of the doctoral project were conducted in a sequential order; i.e., firstly, a face-to-face pilot study of CBT for AF (AF-CBT), then a pilot study of the treatment protocol delivered via internet and finally evaluating the protocol in a randomized controlled trial (RCT). Each study was designed to gain clinical and procedural experiences and apply these experiences to the following study. In addition to the clinical trials, a mediation analysis on the collected data from the RCT was conducted to further explore psychological mechanisms of change in CBT for AF. The aims of the studies are described below.

3.1 STUDY I

The aims of Study I were to develop an exposure-based, AF-specific CBT protocol for patients with paroxysmal AF and to assess if the treatment was feasible, acceptable and potentially efficacious.

3.2 STUDY II

The aims of Study II were to evaluate the efficacy, feasibility and safety of internet-delivered AF-CBT in preparation for a forthcoming RCT. The hypothesis was that the treatment would be feasible and potentially effective based on the results in Study I. Additional aims of the study were to investigate changes in objectively measured AF burden as well as to explore potential mediators of treatment effect on AF-specific QoL.

3.3 STUDY III

The aims of the Study III were to evaluate the effectiveness of exposure-based, internet-delivered AF-CBT compared with a waitlist control group that was offered standardized AF education in an RCT, and to explore changes in objective AF burden. Our hypothesis was that AF-CBT would lead to superior improvements than the control group.

3.4 STUDY IV

Study IV was based on data from the RCT and its aim was to investigate psychological mediators (i.e., cardiac-related fear, hypervigilance, avoidance and stress) of the treatment outcome. We hypothesized that improvements in AF symptoms and AF disability would be mediated through changes in cardiac-related fear/attention and avoidance behavior.

4 EMPIRICAL STUDIES

4.1 STUDY I: EXPOSURE-BASED THERAPY FOR SYMPTOM PREOCCUPATION IN ATRIAL FIBRILLATION: AN UNCONTROLLED PILOT STUDY

Aim

The aims of the study were to develop an exposure-based AF-specific CBT protocol for patients with paroxysmal AF and to assess if the treatment was feasible, acceptable and potentially efficacious.

Methods

The study was an uncotrolled pilot study that included 19 patients diagnosed with symptomatic paroxysmal AF. The CBT treatment lasted for 10 weeks and was delivered in a traditional face-to-face format at the Karolinska University Hospital. The intervention was tailored to AF over the course of the treatments based on clinical presentation. The study design included assessments at pre-treatment, post-treatment and six-month follow-up. Piecewise-linear mixed models were used to estimate within-group effects from baseline to post-treatment and from post-treatment to six-month follow-up. Effect sizes were calculated using Cohen's d (71) where small, medium and large effect sizes are proposed to correspond to d = 0.20, 0.50, and 0.80, respectively. The primary outcome was The Atrial Fibrillation Effect on QoL (AFEQT), which measures self-reported AF symptoms and AF-specific QoL (87). Secondary outcome measures included self-reported frequency and severity of AF symptoms, general anxiety, depression, stress and health-related QoL. Adherence (e.g., session attendance and engagement with exposure exercises) and satisfaction with the treatment were used as measurements of feasibility and acceptability.

Main Results

We observed large treatment effects in self-reported AF-specific QoL and AF symptoms (Cohen's d=1.54; p<. 001) post-treatment, as measured by the primary outcome AFEQT. Improvements were sustained at six-month follow-up. Furthermore, we observed large pre- to post-treatment effects in self-reported severity and frequency of AF symptoms. At post-treatment, we observed moderate to large significant improvements the rest of the outcome measures. At six-month follow-up, we although observed a decline in treatment effects. The reported treatment satisfaction was high and all participants completed the treatment.

4.2 STUDY II: INTERNET-DELIVERED EXPOSURE-BASED THERAPY FOR SYMPTOM PREOCCUPATION IN ATRIAL FIBRILLATION: UNCONTROLLED PILOT TRIAL

Aim

The aims Study II were to evaluate the efficacy, feasibility and safety of internet-delivered AF-CBT. Additional aims of the study were to investigate potential changes in objectively measured AF burden as well as to explore potential mediators of treatment effect on AF-specific QoL.

Methods

In an uncontrolled pilot study, 19 patients diagnosed with symptomatic paroxysmal AF underwent internet-delivered CBT for 10 weeks. The treatment was therapist guided and included exposure to physical sensations, exposure to avoided situations and behavioral activation. During the study, participants completed weekly self-assessments and handheld ECG measurements with symptom registration at pre-treatment, post-treatment and at six-month follow-up. Piecewise-linear mixed models were used to estimate the means and Cohen's *d* to calculate effect sizes. The primary outcome was AFEQT and secondary outcomes included self-reported frequency and severity of AF symptoms, health care visits, cardiac anxiety, depression, stress and general QoL. Feasibility was assessed with regards to treatment satisfaction, number of completed modules and data collection on adverse events.

Main results

Large within-group improvements were observed in AF-specific QoL (Cohen's d=0.80; P<. 001), and in symptom preoccupation (Cohen's d=1.24; P<. 001). The results were sustained six months after the treatment had concluded. Eighty-four percent of the participants were considered treatment completers. Treatment adherence as well as satisfaction with treatment were high. There were also very few and transient adverse events. At six-month follow-up we saw an increased AF burden, as measured by ECG. Interestingly, we observed a significant decrease in participants' overestimation of AF symptoms post-treatment and at six-month follow-up. Exploratory within-group mediation analysis indicated that reduction in symptom preoccupation mediated the effect of internet-CBT on AF-specific QoL.

4.3 STUDY III: INTERNET-DELIVERED COGNITIVE BEHAVIORAL THERAPY FOR SYMPTOM PREOCCUPATION IN ATRIAL FIBRILLATION: A RANDOMIZED CONTROLLED TRIAL

Aim

The aims of Study III were to evaluate the effectiveness of exposure-based internet-delivered AF-CBT compared with a waitlist offered AF education and to explore changes in objective AF burden.

Methods

We included 127 patients diagnosed with paroxysmal symptomatic AF who were randomized to 10 weeks of AF-CBT (n=65) or to an AF education waitlist (AF-EDU; n=62). Participants completed self-assessments pre-treatment, weekly during treatment, post-treatment and at three-month follow-up, along with continuous ECG measurements (e-patch) over five days to evaluate AF burden at the main assessment points. The primary end point was AF-specific QoL measured by AFEQT three months post-treatment, after which patients in the AF-EDU group were crossed over to AF-CBT. Secondary outcomes included self-reported frequency and severity of AF symptoms, AF health care visits, cardiac anxiety, depression and general QoL. The AF-CBT group was also evaluated six and 12 months after treatment. The outcome analyses were based on an intention-to-treat, and we used hierarchical linear mixed-effect modeling to estimate if there was a significant interaction effect between group and time. Effect sizes were calculated using Cohen's *d*.

Main Results

AF-CBT led to a large and significant improvement in AF-specific QoL. The mean QoL score using AFEQT was 62.4 at baseline and increased by 21.0 points in the AF-CBT group compared with 6.0 points in the AF-EDU group (95% CI in difference: 10.1-19.8; *P*<.001) (Figure 3). AF-CBT also showed significant improvements in all the secondary outcomes compared with the control group; e.g., AF symptoms frequency and severity (*P*<.001), symptom preoccupation (*P*<.001), general QoL (*P*<.001), and AF-specific health-care (*P*<.0.027). The results were sustained 12 months after treatment. With regards to objective AF burden as measured by ECG, we observed no significant difference between the groups at the primary endpoint. Figure 3 displays the change in AFEQT score over the study period.

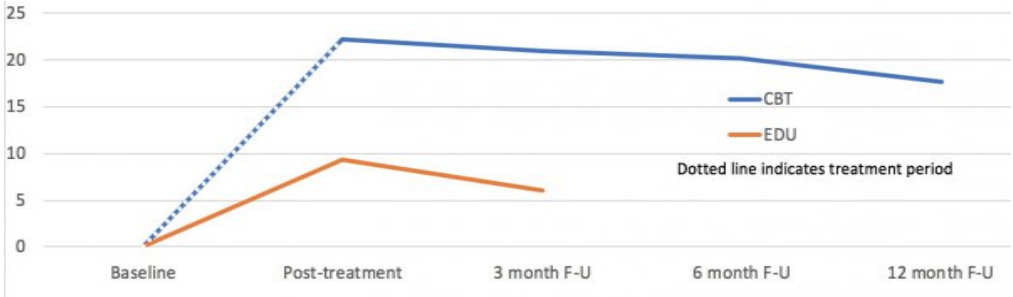

Figure 3. Change in AFEQT score over study period.

4.4 STUDY IV: THE ROLE OF CARDIAC-RELATED FEAR, HYPERVIGILANCE AND AVOIDANCE BEHAVIOR IN EXPOSURE THERAPY FOR ATRIAL FIBRILLATION: A MEDIATION ANALYSIS

Aim

Study IV was based on data from the RCT in Study III, and its aim was to investigate psychological mediators (i.e., cardiac-related fear, hypervigilance, avoidance and stress) of the treatment outcome.

Methods

The study was based on data from the RCT (Study III; N=127) that evaluated AF-CBT compared with a waitlist offering AF education. The main outcome variables (AF symptoms and AF disability) and the putative mediators (cardiac-related fear/hypervigilance, avoidance and stress) were measured weekly throughout the treatment.

Parallel process growth models were used to estimate the effect of the treatment and putative mediators on the outcome. We also used a random cross-lagged panel model to assess the direction of change; i.e., if week-by-week change in the putative mediator preceded the within-individual week-by-week change in the outcome.

Main results

Results from parallel process growth models indicated that improvements in cardiac-related fear/hypervigilance and avoidance behavior, but not perceived stress, mediated the controlled effect of AF-CBT on both AF symptoms and AF disability. However, in random-intercepts cross-lagged panel models of the within-individual week-by-week interrelationships of potential mediators and outcomes, cardiac-related fear/hypervigilance was the only mediator in which changes were systematically predictive of subsequent changes in AF symptoms. Furthermore, avoidance behavior was the only mediator in which changes were systematically predictive of subsequent changes in AF disability.

4.5 PARTICIPANTS

The participants in Study I and II were referred by cardiologists in the greater Stockholm area and then further assessed by the study team consisting of a cardiologist and clinical psychologist before entering the study. Participants in Study III were recruited nationwide by patient self-referral in response to advertisements in daily press and on social media. After an online eligibility screening, participants underwent a cardiac assessment by a cardiology nurse and a cardiologist at Karolinska University Hospital as well as a psychological assessment by a clinical psychologist. Eligible criteria for Studies I-III are presented in the table below.

The mean age of the participants across the studies ranged from 60.5 to 65.4 years. In Study I, 63% of the sample consisted of men, whereas in Study II and III, 63% and 58%, respectively, consisted of women. Most participants had a university degree, 37–53% were currently employed and 37–59% were retired. The mean duration of AF since the first diagnosis was between 5.6 and 8.3 years and 10–42 % had undergone a previous treatment attempt with catheter ablation. Participants who had previously undergone psychological treatment in some form ranged from 28 to 63%. The baseline mean AFEQT score (AF-specific QOL) ranged from 56.9 to 66.8, corresponding to moderate AF severity.

Table 1. Inclusion and exclusion criteria for Studies I-III.

Inclusion criteria	**Exclusion criteria**
(A) paroxysmal AF with an average of ≥1 AF episode(s) per month.	E) heart failure with a left ventricular ejection fraction ≤35% or significant valvular disease.
(B) optimal medical care according to current clinical guidelines .	F) planned ablation for AF or ablation within three months before assessment.
(C) symptoms experienced as troubling or causing limitations in daily activities (i.e., European Heart Rhythm Association (EHRA) class ≥ IIb (88).	G) other severe medical illness or any medical restriction to physical exercise.
(D) aged 18-75 years.	H) other severe psychiatric disorder, risk of suicide, alcohol dependency or concurrent psychological treatment.

4.6 THE TREATMENT: EXPOSURE-BASED AF-CBT

In the treatment, we used an exposure-based approach specifically targeting symptom preoccupation and hypothesized to play a role in AF-related disability. The intervention used in the Studies (I-III) aimed to reduce fear and hypervigilance of AF symptoms and AF-related avoidance behavior.

The following components were included in the treatment: i) education on AF (pathophysiology and medical treatment) and the negative cycle of cardiac-related fear, hypervigilance and avoidance behavior; i.e., symptom preoccupation; (ii) self-observation exercises (i.e., observing cardiac-related symptoms, thoughts, emotional responses and behavioral responses) as planned exercises and when experiencing symptoms. The labeling of internal cardiac-related stimuli aimed to increase tolerance of bodily symptoms; it also guided participants to willingly focus on thoses symptoms, thus enhancing the effect of exposure; (iii) exposure to cardiac-related physical sensations by conducting interoceptive exposure exercises such as inducing palpitations by running on the spot, focusing on the heart while lying on the left side or inducing dyspnea by over-breathing. Participants were instructed to repeat the exercises until symptom fear was significantly reduced; (iv) in-vivo exposure to avoided activities and situations in which symptoms are anticipated or while experiencing symptoms. The varied forms of exposure were often used together, and we also encouraged participants to apply the self-observation exercise while conducting exposure or while experiencing AF symptoms; (vi) reduction or removal of excessive symptom controlling behaviors, such as gradually reducing pulse checking; (vii) behavioral activation, where patients worked towards increasing valued behaviors within life areas impaired by AF; (viii) relapse prevention and how to maintain an active lifestyle if or when experiencing an increase in AF symptoms. .

4.7 MODE OF DELIVERY AND ADAPTATIONS OF THE TREATMENT

The CBT treatment in Study I was made up of 10 weekly face-to-face sessions with homework assignments at the department of cardiology, Karolinska University Hospital. The intervention was derived from an exposure-based CBT protocol for IBS targeting gastrointestinal-specific anxiety and avoidance behavior (71,72) and tailored to AF based on the participants' responses to the treatment and clinical presentation. The internet-delivered treatment in Study II and III consisted of six interactive treatment modules with homework assignments. After the fifth module, participants worked with the exercises continuously and reported weekly to their assigned therapist. In the last week of the treatment, participants worked with a relapse prevention module. Therapist support was provided via written feedback on the assignments within the online treatment platform. The therapist could consult the study cardiologists with regards to specific questions about how to conduct an exposure exercise in a safe manner or questions on the participants' physical health.

For Study II, the treatment was adapted to an internet format and then further revised and streamlined for Study III. Most of the participants had successfully conducted therapist-lead exposure exercises, such as running stairs and increasing their heart rate, at the site. In Study

II, the protocol was designed to maximize the likelihood that the participants would conduct exposure exercises on their own with an extensive rationale on how to conduct exposure exercises, clinical vignettes and case examples, as well as information on safety parameters and directions on how to engage partners in the treatment. For example, we provided a rationale to the participants on how AF symptoms could be viewed as an occasion to apply new skills gained via the treatment. As a safety precaution and as a way to help participants differentiate between cardiorespiratory symptoms and symptoms that require medical attention, all participants were informed that if they experienced sensations of fainting, syncope or exercise-induced chest pain ,they should cease the exposure exercise and consult their treating physician. Because we had observed an overall trend of decline in treatment effect in Study I at follow-up, we further developed the module on relapse prevention in the final step and included strategies to address potential progression of AF.

For the treatment protocol in Study III, we further adapted the protocol and made it even more streamlined towards exposure exercises. We commenced with exposure exercises earlier on in the treatment (session 3), we also used fewer but more cardiac-specific interoceptive exposure exercises, such as lying on the left side and observing the heart for three minutes, to enhance exposure and tolerance of the phobic stimulus; i.e., the heart. Furthermore, we expanded the rationale of exposure to include a range of negative affects (e.g., irritability, discomfort) in response to AF and also included examples of habitual avoidance to be able to capture a broader range in the clinical spectra. We also created a list of AF-related controls and avoidance behaviors, where participants mapped their behaviors out in session 2 (see Figure 4). The list was used throughout the treatment and later used to track and monitor the progress of the exercises. The list also provided an overview for the therapist to encourage the participants to conduct repeated exposure exercises across a broad range of behaviors, impressing upon the patients the importance of leading a meaningful life with or without symptoms.

Figure 4. Screenshot of AF-behaviors used to monitor exposure exercises.

4.8 SAFETY PARAMETERS AND ETHICAL CONSIDERATIONS

AF is associated with both cardiovascular conditions as well as a variety of psychological comorbidities, and when conducting these interdisciplinary treatment studies several ethical considerations in this doctoral project have been taken into account.

The study team thoroughly worked through the eligibility criteria for the patients participating in the treatment to maximize patient safety. The inclusion criteria for patients consisted of some of the following: that the patients received AF care according to current guidelines; that they did not suffer from severe cardiovascular disease (heart failure with severe systolic dysfunction (ejection fraction $\leq 35\%$)); that they did not have significant valvular disease or other severe medical illnesses that may restrict the patients' ability to be physically active; or that they had a severe psychiatric condition or alcohol dependency. To ensure these eligibility criteria were met, the inclusion procedure comprised both a cardiac and psychological assessment. All patients in the studies underwent a cardiac assessment by the study cardiologist (Studies I and III) or by the referring cardiologist (Study II), as well as a structured psychological assessment by a clinical psychologist. The cardiac assessments included an echocardiogram, ECG and blood pressure measurement. Documentation of the AF diagnosis was also reviewed and approved by a cardiologist belonging to the research team before a decision on inclusion was made. The treating psychologists received training in AF by the study cardiologist and were able to consult the study cardiologists at any given point during the treatment.

Engaging in the CBT treatment includes physical activity which may lead to an increased heart rate and give symptoms reminiscent of AF episodes. Importantly, physical activity is recommended in treatment guidelines and is not considered to imply any risk for AF patients included in the study. Although as a safety precaution, we instructed participants to stop the exposure exercises if they experienced exercise-induced chest pain, syncope or a sensation of fainting and contact a physician before proceeding. They were also informed that they should follow their treatment as usual and that their treating physician had continued responsibility for their medical treatment. The study design, with weekly assessments and the continuous contact with the patient, provided the clinical psychologist with good control over progress in treatment. Furthermore, daily online contact in the internet-delivered format provided the participants and psychologist the opportunity to communicate on a regular basis and therefore identify any negative changes in physical or mental health.

The research group carefully selected well-known and validated assessment tools to reduce the burden of filling measurements. All self-rated measures were completed online and the data was securely stored in accordance with applicable laws and regulations. Finally, all the studies included in this doctoral project were registered in the ClinicalTrials.gov trial registry, and all studies will be reported in accordance with the CONSORT statement for non-pharmacological trials and approved by the Regional Ethical Board, Stockholm, Sweden. Overall, the ethical aspects of the studies were thoroughly assessed by the research group, keeping the participants' integrity and safety in focus.

5 DISCUSSION

Within the scope of this thesis, a novel exposure-based and internet-delivered CBT protocol was developed to improve QoL in patients with symptomatic paroxysmal AF. Based on the experience from two pilot studies showing the feasibility and efficacy of AF-CBT in a face-to-face and internet-delivered format, an RCT was conducted demonstrating significant improvements in AF-specific QoL, self-reported AF symptoms and symptom preoccupation in addition to a broad range of secondary outcomes. The participants demonstrated high adherence and treatment satisfaction. Furthermore, the reduction of symptom preoccupation mediated the treatment effect of self-reported AF symptoms and disability. The findings are further discussed below.

5.1 IS EXPOSURE-BASED AF-CBT ACCEPTABLE, FEASIBLE AND SAFE FOR PATIENTS WITH AF?

When we started this project, CBT had never been evaluated in the treatment of AF. At the start of Study I, we were uncertain how patients would respond to CBT for their arrhythmia, a condition with a well-established pathophysiology, commonly not considered for psychological treatment. Previous research had shown that exposure-based CBT had been efficacious and acceptable for patients with other somatic disorders, and since anxiety and psychological distress were prevalent in AF, it made clinical sense to explore the effect of exposure-based CBT for AF patients.

We conducted two pilot studies to build clinical and procedural knowledge on how to best treat AF with CBT. In Study I, the treatment protocol was developed based on clinical presentation, and its acceptability and preliminary efficacy was investigated. In Study II, the treatment protocol was further revised and adapted to an Internet format. Finally, in Study III the treatment was further tailored for the AF population and was evaluated with regards to its efficacy and acceptability in an RCT.

At post-treatment across the trials, we observed high scores in treatment satisfaction as measured with the Client Satisfaction Questionnaire (CSQ-8; range 8-32 with a higher score indicating greater satisfaction): from Study I, 32 points; Study II, 25 points; and Study III, 26 points corresponding to “very satisfied” with the treatment, with a slightly higher score in the face-to-face-treatment. Furthermore, the large majority of participants rated that the treatment helped them to manage their AF symptoms more effectively. Across the trials (Study I-III), we found adherence to the treatment to be high, with 83-100% of the participants completing the treatment, indicating that the treatment was acceptable. The reported adherence to the treatment is considerably higher than the 58% adherence that has been reported in adult meta-analysis of internet-delivered CBT (89). The high treatment satisfaction and adherence are important indicators that exposure-based CBT is a feasible and acceptable treatment for AF patients.

No adverse cardiac events were reported during the course of the treatments or when patients were conducting exposure exercises. There were very few reported general adverse events from

participating in Study I-III; e.g., 4 out of 65 patients in the AF-CBT group in the RCT reported increased cardiac attention or stress due to the study procedure with mild and transient adverse effects. This suggest that the use of exposure-based interventions, both interoceptive and in-vivo, are both safe and acceptable for the target group.

The two pilot studies provided evidence for the feasibility, acceptability and safety of the exposure-based treatment protocol which was later confirmed in the RCT. In summary, the patients' high adherence to and satisfaction with the treatment along with the positive results obtained in multiple domains of AF disability and limited reports of adverse events, indicate that exposure-based AF-CBT is a safe and acceptable treatment option for AF patients.

5.2 IS AF-CBT EFFECTIVE FOR PATIENTS WITH AF?

Exposure-based AF-CBT was shown to be effective (Study I-III) when delivered face-to-face and via the Internet. When investigating the efficacy of AF-CBT compared with a waitlist offered standardized AF education, we observed superior improvements for the treatment group on the primary outcome, AF-specific QoL measured by AFEQT and across the secondary outcomes of symptom preoccupation, self-reported frequency and severity of AF symptoms, general QoL, depression, and health care consumption. The treatment effect was maintained 12 months after the treatment. The mean summary AFEQT score corresponded to moderate AF severity at baseline, and at post-treatment and 12-month follow-up it corresponded to mild AF severity. The effects obtained on the primary outcome are comparable to changes achieved in AF-specific QoL in recent rhythm control (medical therapy) and ablations trials (54). Furthermore, the effect sizes obtained are also in line with effects of internet-delivered exposure-based CBT for other somatic conditions, including cardiac disease (90,83,84).

The internet-delivered treatment may be considered a cost-effective alternative, with therapist time ranging from a weekly mean of 5.7–9.5 minutes per patient in Study II and III (compared with approximately one hour per week in face-to-face CBT). The internet-delivered format provides high accessibility for patients, and the low therapist time expended offers an opportunity to treat a large number of patients. The treating psychologists can be located virtually anywhere, and internet-delivered AF-CBT also allows for centralizing the expertise necessary for delivering safe treatments in collaboration with cardiologists.

Throughout the clinical trials, we observed medium to small effects on depression, which may be explained by average baseline scores below clinical ranges (91). This leaves little room for improvement and thus smaller effect sizes. Depression and perceived stress may be secondary to symptom preoccupation in AF, further emphasizing the importance of targeting disease-specific mechanisms of disability in AF. Paroxysmal AF has been associated with high healthcare utilization and costs (21). Helping patients develop strategies to handle their symptoms rather than repeatedly consulting the healthcare system may help reduce these costs. AF-CBT showed the potential to reduce healthcare consumption; more specifically, we observed that AF-CBT led to a significant reduction of cardiac-specific health care seeking in

Study III, where patients consumed 56% less AF-specific health care compared with the control group.

We observed an increase in the objectively measured AF burden (Study II). In Study III, no difference in AF burden was observed between the groups at three-month follow-up and, over the whole sample, there was a tendency towards an increased AF burden. These results indicate that AF-CBT does not affect the underlying disease, but despite a tendency of increased AF burden, which is expected since the natural course of AF is associated with a gradual increase of AF burden over time (11), participants were still able to achieve large improvements in QoL and symptom preoccupation. Furthermore, we observed low rates of reported deterioration in cardiac health in the studies at six-month follow-up (Study I and II) and at 12 months after the treatment had concluded (Study III). In Study III, the reported deterioration in cardiac health in AF-CBT was low and compared favorably with the control group at 12% and 24%, respectively, and there were few changes in medication and cardiac-related procedures. A possible future direction of research could be to investigate if AF-CBT can have an impact on the preservation of cardiac health and lower the risk for cardiovascular complications.

In summary, internet-delivered exposure-based AF-CBT is effective in improving AF-specific QoL for patients with symptomatic paroxysmal AF already receiving routine care at baseline. We also observed promising results on several outcomes that were sustained 12 months after the treatment.

5.3 DOES REDUCTION IN SYMPTOM PREOCCUPATION MEDIATE CHANGE IN TREATMENT OUTCOME?

Study III was the first RCT of exposure-based AF-CBT targeting symptom preoccupation in AF. Based on the promising effects in that study, we wanted to further explore the processes of change in subjectively rated AF symptoms and disability in Study IV. We also hoped to further understand the psychological factors driving AF-disability beyond the physical disease. We investigated cardiac-related fear/hypervigilance and avoidance, and perceived stress as potential mediators. We observed that reduction in cardiac-related fear/hypervigilance, but not perceived stress, mediated the effect of AF-CBT on AF symptoms and disability. Furthermore, reduction in cardiac-related fear/hypervigilance predicted changes in AF symptoms, whereas reduction in avoidance behavior seemed to be a key mechanism in reducing AF disability.

The results of this study are in line with previous mediation studies of CBT in cardiac disease and noncardiac chest conditions, where reduction in somatic or cardiac anxiety predicted subsequent reduction in cardiovascular outcome and somatic symptoms (92,85). The results are also in line with other mediation analyses of exposure-based CBT, where the reduction in disease-specific anxiety and avoidance behavior was found to mediate the effect on other functional health conditions (89,93,94).

The results from the mediation analysis have clinical and scientific relevance by demonstrating how psychological factors may contribute to symptom severity and disability in AF. The studies also support the treatment model where systematic exposure, both interoceptive and in-

vivo, targeting cardiac-related fear, hypervigilance and avoidance, lead to reduced symptoms and increased functioning in AF. Incorporating the knowledge of the role cardiac-related fear and avoidance behavior play in AF management could lead to the development of more tailored clinical strategies.

5.4 VALIDITY AND GENERALIZABILITY OF THE RESULTS

When interpreting the results of this doctoral project some limitations must be considered. In Study I and II there were no control groups, which limit the causal conclusion on efficacy. The use of a waitlist control in Study III does not control for unspecific treatment effects, such as attention from caregiver. Nevertheless, since the waitlist was offered standardized AF-education, filled in weekly measurements as well as ECG-measurements and knew that they would receive AF-CBT, these factors may have acted as an attention control to some extent.

In Study I and II, recruitment was slow as participants were referred from tertiary care. The slow referral was potentially due to a high workload for clinicians or maybe due to problems identifying which patients would be suitable for CBT. This led us to use self-referral as recruitment method in the RCT, which allowed us in this first evaluation of the efficacy of AF-CBT, to conduct a well-powered study with participants from all over Sweden. There are therefore some points that are interesting to highlight with regards to the generalizability of the results: for example, more than half of the participants in Study I and II had attended some sort of previous psychological counseling. It is therefore a possibility that these patients were more open to psychological treatment than the general AF patient. However, in Study III, which used self-referral, only 28% of the patients had previous experience of psychological treatment. The use of self-referral may have led to a sample that was more similar to AF patients seen in regular healthcare.

With regards to AF severity, we observed that the mean score in AF-specific QoL of the samples in Study I-III corresponded to moderate AF severity, indicating that the participants were representative to average AF patients. In general, the sample also consisted of more women and were younger than the average AF population, which may limit the generalizability of the results on one hand; but on the other hand, since being of female sex and of younger age have been associated with more impaired QoL in AF (24), it is not unexpected that there were proportionally more women in the study samples.

Furthermore, the number of patients in the clinical diagnostic interview in Study III that were assessed with depressed mood (29%) or any anxiety disorders (24%) or any psychiatric comorbidity (in Studies I and II (21-26%)) are comparable with findings investigating elevated levels of anxiety and depression in AF (31). This reflects that the proportion presenting with anxiety and depression in the study is comparable to the average AF population. We also found that 65% of the participants in Study III fulfilled the diagnostic criteria of Somatic Symptom Disorder (SSD), which is a diagnosis characterized by impairments following emotional and behavioral responses to somatic symptoms. The number of participants showing symptom-specific anxiety further strengthens our disease-specific model targeting symptom

preoccupation. When assessing SSD in the general population it has been shown to be more prevalent in patients with underlying medical disorders (95). Whether the proportion of SSD observed in the study corresponds to the general AF population has yet to be investigated; there is no current data available on this matter. Also, assessing if the presence of SSD is a predictor for treatment response could also be of further interest.

Finally, the results from the mediation analysis (Study IV) have to be interpreted with some limitations in mind: for example, the treatment did not target stress and that mediator was primarily included to control for specificity of the proposed mediators. Furthermore, there is no guarantee that the change in the outcome that is explained by the preceding change in the mediator corresponds to the variance explained by AF-CBT. Another limitation is that the CAQ subscale measuring avoidance mostly dealt with avoidance of physical activity, and investigating the broader range of avoidance behaviors that is targeted by AF-CBT would have been preferable to more fully investigate the active treatment mechanism.

5.5 CLINICAL IMPLICATIONS

The observed effects of AF-CBT were achieved in symptomatic patients already receiving medical therapy according to clinical guidelines, which also was reflected in the cardiac parameters of the sample characteristics. This suggests that AF-CBT is an effective treatment and can be used for AF patients presenting with symptom preoccupation despite optimal medical care. We also observed that around 10-40% of the participants in the clinical studies had undergone at least one ablation, indicating that CBT could be suitable option for patients who are still troubled by their symptoms despite invasive therapy. AF-CBT can also function as a treatment option for patients that are not eligible for invasive therapies or as an alternative option based on the patients' preference of treatment.

Our results demonstrate that psychological factors may contribute to symptom severity and disability. This knowledge should ideally also be integrated in AF management; in, for example, standardized AF education when patients are being diagnosed with AF as well as to identify symptom preoccupation in AF patients. Another way to integrate this in clinical practice could be to use the already well established EHRA scale classification class ≥IIb (88); i.e., symptoms that trouble the patient or cause limitations in daily life. We used the EHRA scale classification class ≥IIb (88) as an inclusion criterion across the clinical trials and suggest that patients fulfilling EHRA class IIb also might be presenting with patterns of symptom preoccupation. EHRA class IIb has shown to correlate with moderate AF severity (AFEQT (88)) as seen in our study samples, and could be used as clinical indication for healthcare professionals to further screen patients for psychological impairments or for referring to AF-CBT.

This novel interdisciplinary approach to AF demonstrates increased QoL and reduced health care utilization in a safe manner. In order to have a positive impact on patient wellbeing and routine clinical practice, we hope to make the treatment accessible for the target population on a large scale by implementing and disseminating AF-CBT within routine care. I think that AF-

CBT for AF patients presenting with symptom preoccupation could be used as a treatment option in different steps of AF care: for patients newly diagnosed with AF; following, for example, invasive therapy; or as an addition to routine AF care. The manual-based structured format allows for a brief training period for psychologists who could then deliver AF-CBT via a national Internet treatment unit, in collaboration with a cardiologist assigned to oversee the medical safety parameters.

5.6 FUTURE DIRECTIONS

This doctoral project has shown promising effects in the first evaluation of internet-delivered exposure-based AF-CBT for AF patients with symptom preoccupation. We used a low-intensity control condition in the early phase of evaluating this novel treatment to minimize the risk of committing Type II-errors. But in a coming trial, we will use an active control group to further evaluate the treatment protocol and isolate treatment-specific effects. We are planning to conduct an RCT in the fall of 2021, where AF-CBT will be compared with a stress management intervention. This will further help us understand treatment-specific mechanisms and to evaluate the long-term effects of AF-CBT compared with an active control group.

In addition to the mediation analysis, it would be of interest to further explore the active mechanism of the treatment, and to which magnitude of change are the treatment components attributable (e.g., interoceptive exposure, exposure in-vivo or self-observation [i.e., affect labeling]) by using a dismantling design. In addition to this, it might be effective to conduct prediction analysis to further investigate for whom the treatment is effective, with regards to AF severity and psychological correlates, for example. This knowledge could further be used to evaluate AF-CBT in a brief and easily applied format consisting of, for example, one session of psychoeducation and interoceptive exposure in conjunction to receiving the AF diagnosis, to possibly minimize the development of symptom preoccupation.

Extending the follow-up time could also provide us with information on if and when the treatment effects start to decline and whether, for example, a booster session could benefit patients. Furthermore, empirically based insight into psychological processes that shape long-term outcomes could be explored using registry data. For example, it would be interesting to explore if AF-CBT has the potential to reduce other cardiovascular risk factors by collecting follow-up data from patient registries.

Encouraged by the results of CBT in AF, we have adapted the exposure-based treatment to two other cardiac conditions where symptom preoccupation may affect the clinical course. We are currently investigating exposure-based CBT for premature ventricular contraction (extra heartbeats) and in patients following myocardial infarction. A long-term goal would be to build a similar research program and interdisciplinary knowledge base for a broad range of cardiac diseases in an effort to bridge the treatment gap for cardiac patients in need of psychological treatment.

6 CONCLUSIONS

Internet-delivered AF-CBT is a feasible and effective treatment for AF patients that significantly improved AF-specific QoL, self-reported AF symptoms, symptom preoccupation and health care consumption in patients with symptomatic paroxysmal AF already receiving routine AF care. The effects were sustained 12 months after the treatment had concluded. Exposure-based AF-CBT delivered via the Internet has the has the capacity to ameliorate the well-being of a large group of patients who do not sufficiently improve from current treatment methods. Symptom preoccupation, i.e., cardiac-related fear, hypervigilance and avoidance, is an important target for treatment, mediates the reduction of symptoms and increases functioning in AF. The results in this thesis support the integration of psychological evaluation and treatment in AF management.

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